REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1, 4, 7-9, 13, 16, 19, 20, 22-26 and 28-31 are pending in the application. Claims 1, 7, 16, 19 and 25 are amended, claims 6, 17 and 27 are canceled, and new claims 28-31 are added by the present amendment.

Support for each of the amendments and new claims can be found in the specification at, *e.g.*, paragraph 0011 of the published application (US 2006/0142220 A1).

The amendment of claims herein should not be construed as an acquiescence to any position taken by the Examiner with respect to the scope of the originally-filed or previously pending claims. Rather, Applicants have amended the claims to advance prosecution of the application. No new matter is added by the present amendment.

Interview Summary

Applicants thank the Examiner, the Examiner's supervisor Joseph Woitach, and primary examiner Robert Kelly for taking time to discuss the present Office Action with the undersigned on April 27, 2010, in which both the enablement and obviousness rejections were discussed, as well as proposed claim amendments.

Applicants understand that the amendments to independent claims 1, 16 and 25 will resolve the current rejections under 35 U.S.C. 112, discussed more fully below. Although no formal agreement was reached with regard to the current rejections under 35 U.S.C. 103, Applicants respectfully request favorable reconsideration of the outstanding rejections based on the presently amended claims and the remarks set forth below.

Claim Rejections - 35 U.S.C. §112, 1st Paragraph - Enablement

Claims 1, 4, 6-9, 13, 16-18, 19, 20 and 22-27 are rejected under 35 U.S.C. 112, first paragraph because the specification allegedly does not enable modification of any O-linked carbohydrate moiety other than galactose or Gal(β1-3)GalNAc, or the use of any O-linked carbohydrate modifying enzyme other than ST3Gal I or ST3Gal III. In particular, the Examiner states that given the lack of predictability in the art regarding the functions of various carbohydrate chains that can be modified, one of skill in the art would not be able to determine

the effect of various modifications on the function of the recombinant human C1 inhibitor or other modified glycoprotein with enzymes other than those exemplified, nor the effect that modifications to carbohydrate moieties other than galactose or Gal(β1-3)GalNAc would have on the half-life of the modified glycoprotein. Further, the Examiner states that the art teaches that certain scialylating moieties are species specific, and may cause severe immunological reactions in other species. *See* pages 3-5 of the Office Action.

Applicants have amended independent claims 1, 16 and 25 to indicate that the modified (claims 1 and 25) or removed (claim 16) O-linked carbohydrate comprises Gal(β1-3)GalNAc. Both sialyation and removal of Gal(β1-3)GalNAc structures are exemplified in the specification. *See* Examples 1-4. Neither *in vitro* sialylation nor O-glycosidase treatment had any affect on the protease inhibitory activity of the exemplified glycoprotein (rhCIINH). *See, e.g.*, paragraphs 0027 and 0038. Thus, Applicants submit that any comparable modification, irrespective of the enzyme used to make the modification, will not affect the underlying function of the rhC1INH recited in independent claims 1 and 25. Moreover, Applicants note that no function is claimed with regard to the glycoproteins recited in independent claim 16.

Applicants submit that other enzymes capable of modifying the carbohydrate structure recited in the amended claims were known in the art. For example, Harduin-Lepers *et al.*, *Biochemie*, 83:727-737 (2001) reports sialyltransferases capable of sialylating Gal(β1-3)GalNAc structures to produce the same modification of the exemplified ST3Gal I enzyme. *See* p. 728, "ST3Gal I," "ST3Gal II," and "ST3GalIV." Similarly, Cabezas *et al.*, *Int. J. Biochem.*, 15:243-259 (1983) reports at least three enzymes with N-acetylgalactosaminidase activity. *See* p. 249, 1st column, 2nd full paragraph (discussion of β-N-acetylhexosaminidase enzyme as having β-N-acetylgalactosaminidase activity), and p. 250, 1st column, 2nd full paragraph (discussion of other studies conducted on endo-α-N-acetylgalactosaminidase and α-N-acetylgalactosaminidase). Copies of these two references are provided with the supplemental Information Disclosure Statement submitted herewith.

With regard to the issue of potential immunological reactions raised by the Examiner, Applicants submit that because the sialylation method of claim 25 is performed *in vitro*, one performing the claimed method could choose the sialic acid source (*e.g.*, CMP-sialic

acid), and thereby avoid any unwanted immunological reactions that might otherwise arise from incorporation of an antigenic sialic acid moiety.

In view of the foregoing, Applicants submit that the full scope of the presently claimed invention is enabled by the specification. Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C. §103

Claims 1, 4, 6-9, 13, 16, 17, 19, 20 and 22-27 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over **Wolff** *et al.*, *Protein Expression and Purification*, 22:414-421 (2001) and **Paulson** *et al.*, WO 98/31826. In particular, the Examiner states that Wolff teaches the production and purification of recombinant C1 inhibitor, the differences between native and recombinant molecules in regard to glycosylation, and the importance of reduced O-glycosylation in hereditary diseases. The Examiner acknowledges that Wolff does not teach extending the circulatory half-life of recombinant C1 inhibitor via sialylation of O-linked carbohydrates. The Examiner further states that Paulson teaches increasing plasma circulatory half-life of recombinant glycoproteins via modification of both N- and O-glycosylation moieties by sialylation. Thus, the Examiner concludes that one of skill in the art would have been motivated to modify the recombinant C1 inhibitor of Wolff using the sialylation methods taught by Paulson because the art teaches that it is routine to sialylate terminal galactose residues of N- and/or O-linked carbohydrates to increase their half-life.

Independent Claims 1 and 25

Applicants respectfully disagree. Paulson discusses the importance of N-linked carbohydrate groups to the circulatory lifetime of glycoproteins. In particular, Paulson reports that "[t]he circulatory lifetime of glycoproteins in the blood is highly dependent on the composition and structure of its ***N-linked*** carbohydrate groups" (page 1, lines 16-17; emphasis added), that "maximal circulatory half life of a glycoprotein requires that its ***N-linked*** carbohydrate groups terminate in the sequence *NeuAc-**Gal-GlcNAc***" (page 1, lines 19-20; emphasis added), and that "[f]or this reason, ensuring the presence of terminal sialic acid on ***N-linked*** carbohydrate groups of therapeutic glycoproteins is an important consideration for their

commercial development" (page 1, lines 23-25; emphasis added). Although Paulson reports methods using sialyltransferases capable of sialylating Gal(β1-3)GalNAc structures, nowhere does Paulson mention or suggest that sialylation of O-linked carbohydrates, or particularly the Gal(β1-3)GalNAc structure recited in the presently claimed invention, has an affect on the circulatory life-time of glycoproteins in the blood. In fact, the Examiner has acknowledged that Paulson does not teach the importance of O-linked glycosylation to the circulatory half-life of the protein. *See* paragraph bridging pp. 7-8 of the April 19, 2006 Office Action.

Wolff does nothing to cure this deficiency in Paulson. As acknowledged by the Examiner in the present Office Action, Wolff does not teach extending the circulatory half-life of recombinant C1 inhibitor via sialylation of O-linked carbohydrates. Thus, none of the cited art teaches that sialylation of an O-linked Gal(β1-3)GalNAc structure increases the plasma circulatory half-life of a recombinant human C1 inhibitor, as claimed.

In view of the foregoing, Applicants submit that independent claims 1 and 25, as well as the corresponding dependent claims, are patentable over the cited art for at least the reasons discussed above. Accordingly, Applicants respectfully request withdrawal of this ground of rejection as applied to claims 1, 4, 7-9, 13, 25, and 26.

Independent Claim 16

Independent claim 16 is directed to a method for extending the blood circulatory half-life of a glycoprotein or of a glycoprotein comprising compound via removal of one or more non-sialylated O-linked carbohydrates comprising Gal(β1-3)GalNAc by *in vitro* incubation with an enzyme preparation.

Applicants have been unable to identify any specific discussion in the current Office Action applying the cited art to independent claim 16 or claims depending therefrom.

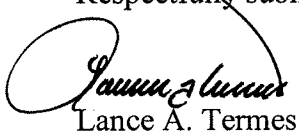
In the interest of being fully responsive, Applicants submit that Paulson does not discuss the removal of non-sialylated O-linked Gal(β1-3)GalNAc structures in any capacity. Moreover, although Wolff reports the removal of O-glycans from the C1 inhibitor for analysis of the presence of O-glycan chains, the removal is performed by contacting the C1 inhibitor with lithium hydroxide (*see* paragraph bridging pp. 416-417), rather than via incubation with an

enzyme preparation, and there is no discussion of extending blood circulatory half-life by making such modifications.

In view of the foregoing, Applicants submit that independent claim 16 and claims depending therefrom are patentable over the cited art. Accordingly, Applicants respectfully request withdrawal of this ground of rejection as applied to claims 16, 19, 20 and 22-24.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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